Popular immunotherapy target turns out to have a surprising buddy

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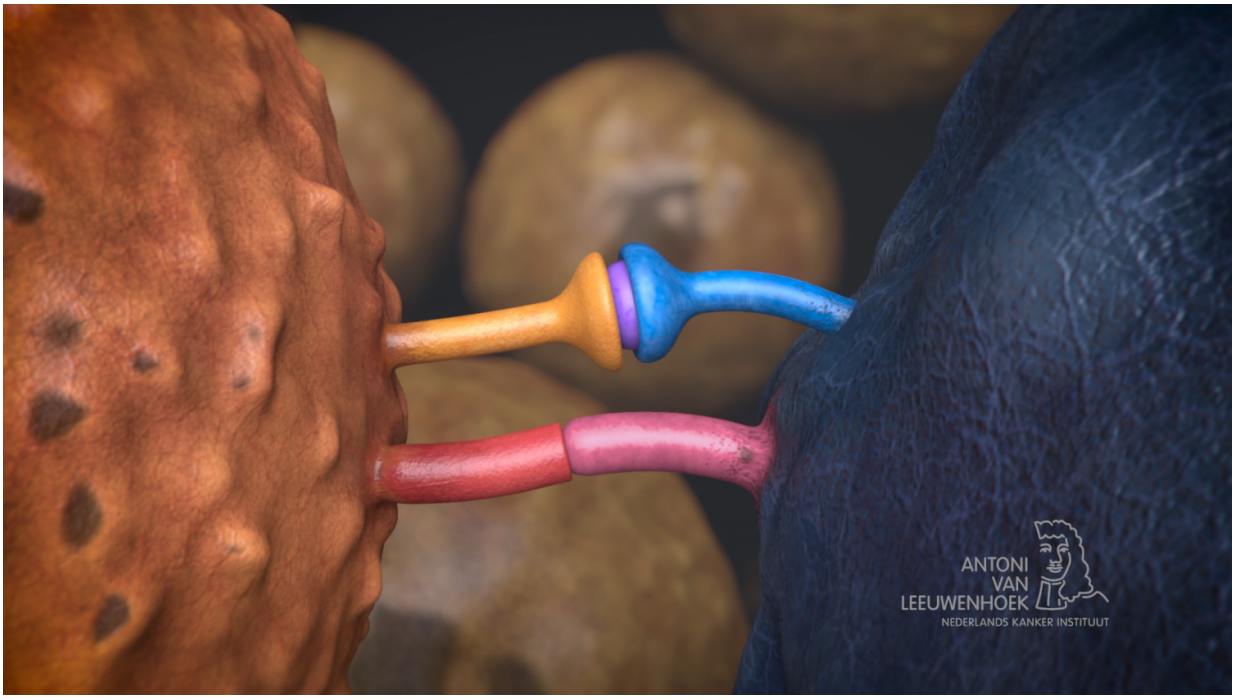


The T-cell receptor (orange) on the T-cell (left) binds a receptor on a cancer cell (right). The cancer cell blocks the T-cell's killing mechanism by binding the checkpoint (red) on the T-cell. Credit: The Netherlands Cancer Institute

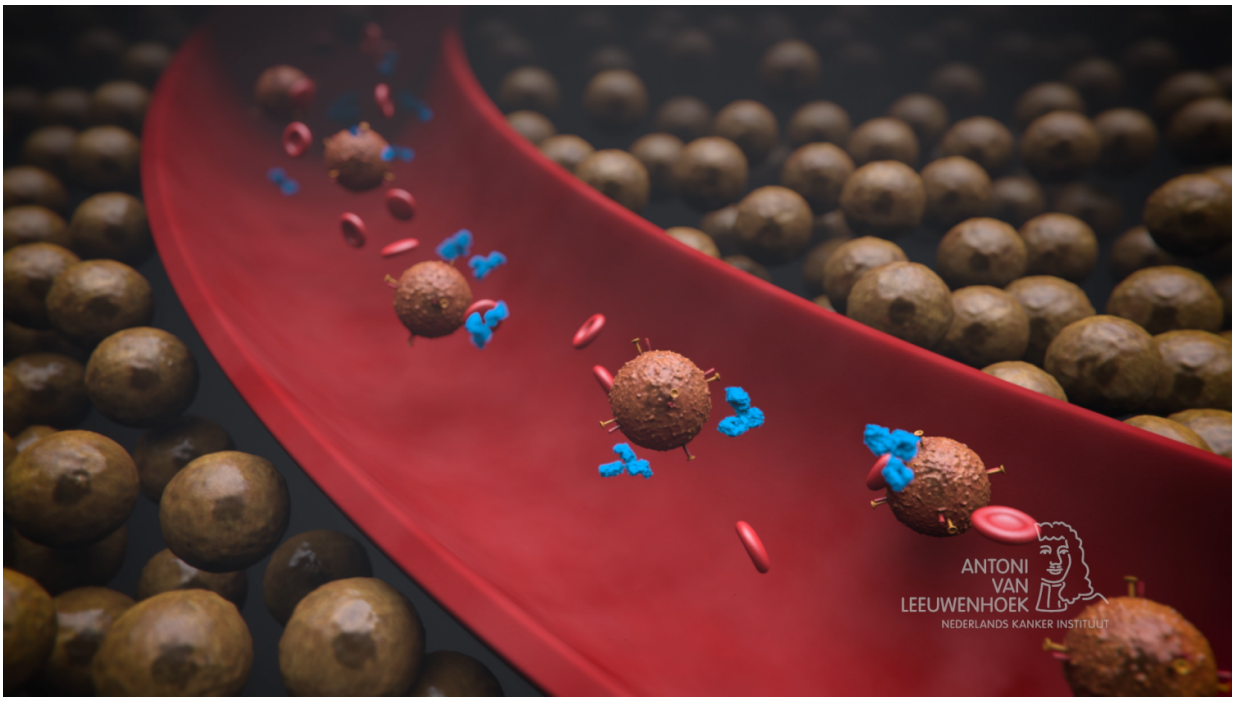
The majority of current cancer immunotherapies focus on PD-L1. This well studied protein turns out to be controlled by a partner, CMTM6, a previously unexplored molecule that is now suddenly also a potential therapeutic target. Researchers from the Netherlands Cancer Institute

publish these findings in the leading journal *Nature* on August 16.

Immunotherapy is an exciting new way of treating cancer. The immune cells that circulate throughout the human body are supposed to attack and eliminate any cancer cells they encounter. However, some cancers have found a neat way to evade this destiny: they abuse a natural brake that is present on immune cells called T-cells. By binding to this so-called checkpoint using a protein called PD-L1, the cancer cell deactivates the T-cell's killing mechanism.

Because of its central role in controlling T cell activity, PD-L1 on cancer cells has become the center of attention in immunotherapy. Treatments that block this checkpoint are already used by patients with, for example, melanoma, lung cancer and renal cancer. In addition, hundreds of clinical studies that are ongoing worldwide investigate these compounds in many other cancer types.

Despite the fact that cancer patients already benefit from these blockers, much about PD-L1 remains unknown. For instance, why do some cancers carry more of this molecule than others? Researchers of the Netherlands Cancer Institute set out on a quest for clues and found an important one. "We always thought PD-L1 was a loner at the cancer cell surface, but it turns out that it binds to another protein", says professor Ton Schumacher. "This other protein, called CMTM6, stabilizes PD-L1 and thereby increases the capacity of cancer cells to inhibit the immune response." Schumacher's group carried out this project in close collaboration with colleagues Thijn Brummelkamp, Jannie Borst and Christian Blank at The Netherlands Cancer Institute, and Albert Heck at Utrecht University.



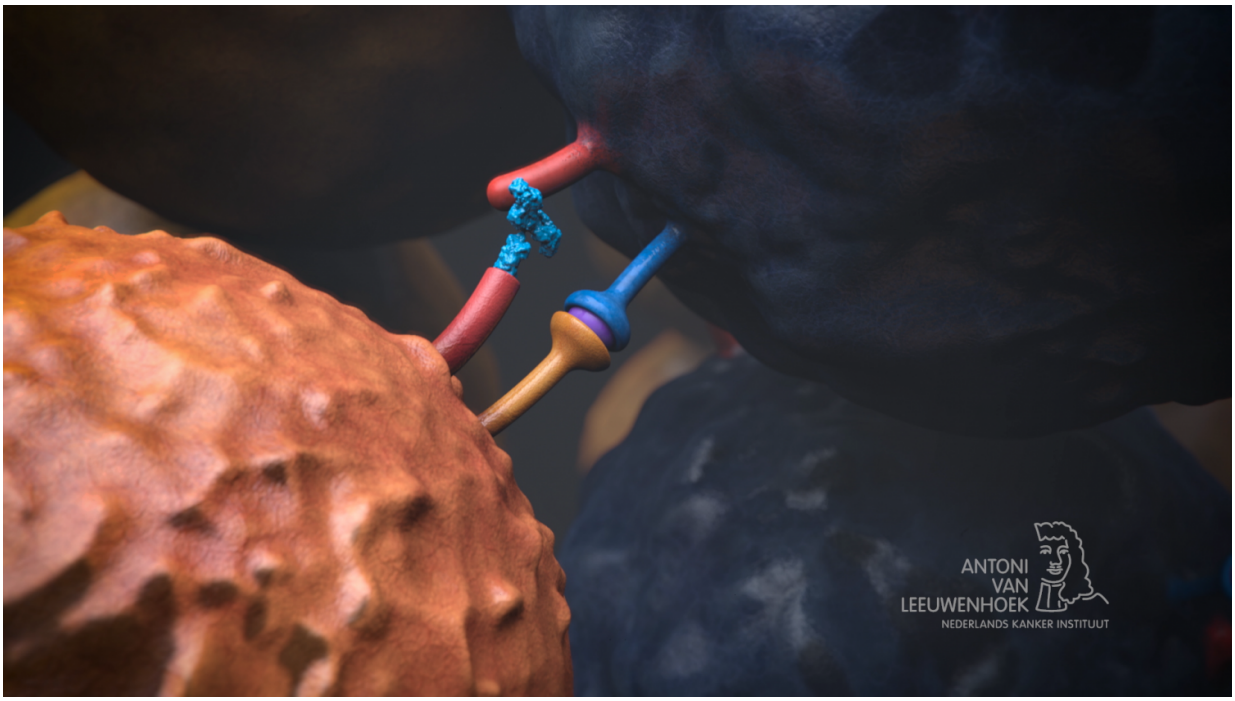
Checkpoint inhibitors (blue) and T-cells (brown) in the bloodstream. Immunotherapy with checkpoint inhibitors is currently used by patients with for example melanoma, lung cancer and renal cancer. Credit: The Netherlands Cancer Institute

In addition to being highly relevant for understanding how the PD-L1-checkpoint works, this discovery might also have uncovered a new target for immunotherapy. Schumacher: "You can imagine that blocking CMTM6 could reactivate immune cells just like the currently used PD-L1 blockers can. Blocking both molecules could even be superior. It remains to be seen whether it will eventually deliver a therapy, but this is clearly something we are eager to test."

The newly identified companion of PD-L1 may also help clinicians predict whether patients will benefit from treatment with checkpoint inhibitors. Schumacher and his colleagues are currently investigating this

in patients who are treated with the current PD-L1-blockers. "The amount of PD-L1 itself can predict treatment success to a limited extent and we have some hope that CMTM6 can improve the precision of this prediction."

Interestingly, a group of Australian and English researchers publish a very similar story about CMTM6 in the same edition of Nature. Schumacher: "Our colleagues used different methods to discover the same process. I think we were both quite happy to see this independent validation."



The checkpoint inhibitor (blue) prevents binding of the checkpoint by the cancer cell so the T-cell can kill the cancer cell. Credit: The Netherlands Cancer Institute

More information: Riccardo Mezzadra et al, Identification of CMTM6 and CMTM4 as PD-L1 protein regulators, *Nature* (2017). DOI: 10.1038/nature23669